REMARKS

Claims 1-4 and 150-167 presently appear in this case. Claims 1-4 have been allowed. Claims 152-155, 158-161 and 164-167 are free of the prior art, but are rejected under 35 U.S.C. §112. The official action of June 10, 2004, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

I. Withdrawal of Finality

Before discussing the substance of the official action, applicant objects to the finality thereof as being premature. As stated in MPEP 706.07(a):

> Under present practice, second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims, nor based on information submitted in an Information Disclosure Statement filed in the period set forth in 37 C.F.R. §1.97(c), with the fee set forth in 37 C.F.R. §1.17(p). ...
>
> A second or any subsequent action on the merits in any application or patent involved in reexamination proceedings should not be made final if it includes a rejection, on prior art not of record, of any claim amended to include limitations which should reasonably have been expected to be claimed.

The present Office action contains, for the first time, two 35 U.S.C. §102 rejections, one based on Bickel et al, and one based on Stern et al. Stern et al was of record during the prosecution of the application that issued as patent 5,688,651 (of which the present is an application for reissue) and is specifically mentioned at column 15, line 35, of the present

application, but has never been cited by the Examiner in this case or applied against the claims. Stern et al was cited by applicant in an Information Disclosure Statement submitted on February 23, 2004. Bickel et al was never previously cited by the Examiner or applicants. While claims 150-167 were new claims presented in applicant's amendment of February 23, 2004, they are not substantially different from previously appearing claims 126-129. Therefore, it cannot be said that applicant's amendment to claim 126 (new claim 150) necessitated the rejection on the basis of Stern et al or Bickel et al, the latter of which had never before been cited of record in the case. Accordingly, the finality of the rejection is premature. Reconsideration and withdrawal of the finality are therefore respectfully urged.

II. **Statements under 37 C.F.R. §1.173(c)**

The following statements are made pursuant to the requirements of 37 C.F.R. §1.173(c). Patent claims 1-4 are pending and have not been changed from the language of these claims as they appeared in the patent. Added claims 5-149 have been cancelled. Claims 150-167 presently appear in this case. Claims 150-167 relate to a pharmaceutical formulation. Attached hereto as Exhibit A is a printout from the internet, showing that the "Dictionary Barn" Medical Dictionary defines "formulation" as:

> <pharmacology> The mixture or prescribed recipe for packaging a protein pharmaceutical, the process of developing such a formulation.

Thus, the term "formulation" is a mixture or prescribed recipe for packaging a protein pharmaceutical, i.e., a unit dosage form.

Furthermore, the formulation contains a "pharmaceutically acceptable carrier". As discussed at column 9, lines 28-31, of the present application:

> The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipients.

III. Summary of the Invention

Briefly, the present invention relates to pharmaceutical formulations comprising an antibody or an antigen binding fragment thereof and a pharmaceutically acceptable carrier.

The antibody and fragment recognize an epitope within residues 1-28 of β-amyloid (claims 150-155 and 162-167) or are obtainable using residues 1-28 of β-amyloid Aβ(1-28) as an immunogen (claims 156-161), and thus recognize Aβ(1-28).

The antibodies and fragments inhibit aggregation of β-amyloid (claims 150-161) or they maintain the solubility of soluble β-amyloid (claims 162-167).

The antibody is preferably a monoclonal antibody (claims 151, 157, 163), and more preferably a human monoclonal antibody (claims 152, 158, 164), a genetically engineered monoclonal antibody (claims 153, 159, 165), or a single chain antibody (claims 154, 160, 166). The β-amyloid is preferably human β-amyloid (claims 155, 161, 167).

IV. Statement under 37 C.F.R. §1.178(b)

The present patent is not and has not been involved in any prior or concurrent proceeding, including interferences, reissues, reexaminations and litigation.

V. Information Disclosure Statement

An Information Disclosure Statement is attached hereto to bring to the examiner's attention three patents which issued subsequent to the date of mailing of the outstanding office action, and that, while not available as prior art, contain experimentation that is evidence of the enabling nature of the present specification.

VI. Supplemental Declaration under 37 C.F.R. §1.175(b)(1)

Since the claims are not being amended herein, a supplemental reissue declaration is not required.

VII. Objection to Previous Information Disclosure Statement

The examiner states that the Information Disclosure Statement filed August 22, 2002, does not include a page 2. Presumably, the examiner is speaking of page 2 of the PTO/SB/08a form that was attached thereto, as the page of that form that was submitted indicated that it was "sheet 1 of 2." The examiner is hereby informed that the reference to "sheet 1 of 2" was erroneous. Only one sheet of PTO/SB/08a was intended to have been submitted. The 13 references submitted with that Information Disclosure Statement correspond exactly to the 13 citations on this form.

VIII. Objection to Claim 164

Claim 164 has been objected to because the text of this claim is not legible. Applicant has been invited to

include a clear copy of claim 164 in the response to this Office action.

The present amendment includes a clear copy of all of the present claims, including claim 164, thus obviating this objection.

IX. **Enablement Rejection**

Claims 150-167 have been rejected under 35 U.S.C. §112, first paragraph. The Examiner contends that the specification, while being enabling for a formulation comprising the antibody AMY33 or a fragment thereof, and a carrier comprising same, does not provide enablement for any other antibodies that recognize an epitope within residues 1-28 of β-amyloid or pharmaceutical formulations thereof. This rejection is respectfully traversed.

First of all, the examiner has apparently failed to appreciate the difference between claims 150-155 and 162-167 versus claims 156-161. In claims 150-155 and 162-167, the antibody "recognizes an epitope within residues 1-28 of beta-amyloid", whereas in claims 156-161, the antibody is "obtainable using residues 1-28 of beta-amyloid as an immunogen". Thus, in the latter claims, the antibody is defined by the process by which it can be obtained, i.e., such is obtainable using a specific beta-amyloid fragment (residues 1-28) as the immunogen, whereas in the former claims, the antibody is defined by the region in beta-amyloid which it recognizes, i.e., the antibody recognizes an epitope within residues 1-28 of beta-amyloid. The examiner's rejection does

not address, and is clearly not appropriate as to claims 156-161.

In any event, the examiner's rejection is believed to be improper as to all of the pending claims because the claimed antigen is fully characterized by a known sequence, i.e., Aβ(1-28). The specification states that the Aβ(1-40) peptide and the Aβ(1-28) peptide were purchased from Sigma Chemical Co., St. Louis, Mo., under catalog numbers A-5813 and A-0184,[1] respectively. The attached pages (Exhibit B) of the Sigma Catalog show that the entire sequence of Aβ(1-28) is provided, i.e., Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys. The catalog also shows the same sequence for the first 28 residues of Aβ(1-40). The catalog also states that the peptide is "synthetic". The sequence of Aβ(1-28) was well-known in the art. Further, the sequence could be readily synthesized by techniques known to those skilled in the art by 1994. Thus, this peptide was clearly known and readily available to the public, and readily synthesizable as of the effective filing date of the present application.

Antibodies can readily be made using this entire known sequence (Aβ(1-28)), or using a fragment thereof containing an epitope within this sequence. Any antibody found to recognize an epitope within residues 1-28 of beta-

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[1] In looking up Aβ 1-28 in the Sigma catalog, it was discovered that the patent has a typographical error (number transposition) in the catalog number. It is not A-1084, but A-0184. Accordingly, this typographical error in the present specification has now been corrected. A copy of the relevant pages of the Sigma Catalog is attached hereto as Exhibit B.

amyloid can then be readily tested by the simple assays, e.g., as described in Example 2 of the present specification, to determine that the antibody inhibits aggregation of β-amyloid or maintains solubility of beta-amyloid, as claimed. This is not an unreasonable amount of experimentation. As stated at MPEP §2164.01 (May 2004):

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. ... The test of enablement is not whether experimentation is necessary, but whether, if experimentation is necessary, it is undue.

In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988), already has held that the amount of experimentation necessary in order to produce antibodies is not undue. If this amount of experimentation is not undue, certainly the simple assays of Example 2 of the present specification to test each of the antibodies found would not be undue experimentation. See also *Ex parte Mark*, 12 USPQ2d 1904 (BPAI 1989), where the examiner argued that it would require undue experimentation to construct the innumerable mutant proteins encompassed by the claims (the claims encompassed modification of any protein which comprises a "non-essential" cysteine residue) and to screen the mutant proteins produced for those which exhibit biological activity after modification as claimed. The Board reversed the examiner's enablement rejection, and held that the examiner improperly relied upon examples in the specification showing biologically inactive proteins having the claimed modification, because such "inactive" mutants are *outside* of the claims (which require biological activity).

The Board held that for a *given* protein having cysteine residues, one skilled in the art would be able to routinely determine whether deletion or replacement of the cysteine residues would result in a mutant protein having biological activity as claimed. Thus, even though antibody 6F/3D (raised against residues 8-17 of Aβ) described in the present application does not inhibit aggregation of Aβ, such is irrelevant to enablement of the present claims. This is because the "inactive" 6F/3D antibody is outside of the scope of the present claims which require that the antibody inhibit aggregation.

Furthermore, the publications of record cited in applicant's previous amendment filed February 23, 2004, confirm that the process described in the present application can be used to identify other antibodies, specifically antibodies 10D5 and 6C6, that inhibit β-amyloid aggregation. As discussed in the amendment filed February 23, 2004:

> Hanan (1996)[3] confirms the results in the Solomon application and Solomon (PNAS 1996). That is, when using the same heat-induced aggregation assay and antibodies 10D5 and 6C6 (both raised against amino acids 1-28 of Aβ (Bard et al (2003)[4]; 2H3 (raised against amino acids 1-2 of Aβ), and 1C2 (raised against amino acids 13-28 of Aβ), it was found that antibodies 10D5 and 6C6 were most effective at preventing/inhibiting the formation of aggregates (see Figure 1 thereof). [Footnotes Omitted]
>
> Moreover, the electron micrographs of Figure 2 of Solomon (PNAS 1996) clearly demonstrate that AMY-33 converts fibrillar Aβ to an amorphous state, and prevents/inhibits aggregation. Similarly, the electron micrographs of Figure 1 of Solomon (Fisher 1998)[5] confirm these results using 6C6 (raised against amino acids 1-28

> of Aβ), i.e., this antibody also prevents/inhibits aggregation. [Footnote Omitted]
>
> Solomon (PNAS 1997)[6] confirms the results in the Solomon application and Solomon (PNAS 1996). That is, when using a similar assay (but that measures disaggregation), and antibodies 6C6 (raised against amino acids 1-28 of Aβ; (Bard et al (2003)); 1C2 (raised against amino acids 13-28 of Aβ), and 14C2 (raised against amino acids 33-40 of Aβ), it was found that antibody 6C6 was most effective at solubilizing Aβ (see Figure 1 thereof). [Footnote Omitted]

The examiner cites Walker et al (1994) as teaching that antibody 10D5 does not disaggregate or inhibit Aβ aggregation. However, as explained in applicant's amendment of February 23, 2004, Walker merely relates to *in vivo* imaging of Aβ deposits in the brain. Walker did not look for, much less carry out any experiments to measure disaggregation or prevention/inhibition of aggregation. The evidence of record submitted by applicant, i.e., Hanan et al (1996), Fisher et al (1998), and the Solomon declaration of record, clearly show that 10D5 does inhibit aggregation of Aβ. It is not understood why the examiner continues to hold that Walker teaches otherwise. It does not. In Walker, the monkeys were sacrificed shortly after the experiment, so there was no long term study. The fact that the antibody bound to plaque is not evidence that there was no disaggregation. The specific evidence as to the measurement of the effectiveness of 10D5 in inhibiting aggregation must, in fairness, be considered in conjunction with Hanan et al (1996) and Fisher et al (1998) and the Solomon declaration. Upon consideration of all the evidence of record, it is clear that 10D5 is an antibody that

would fall within the scope of the present claims and can be identified as having the desired properties.

With respect to the *Wands* factors, the state of the prior art is that the production of antibodies was well known, as evidenced by *In re Wands* itself. Concerning the breadth of the claims, and the nature of the invention as a therapeutic, the claims are not broader than enablement. As discussed above, the antibodies may be raised against a well-defined antigen (residues 1-28 of beta-amyloid), and fragments thereof can readily be used as an immunogen to raise antibodies without undue experimentation. To use the same is certainly within the capacity of a standard research organization and would not involve undue experimentation. Once antibodies are found that recognize the antigen, the aggregation inhibition and solubility maintaining assay as disclosed in the Example 2 of the present specification can be conducted in a very standard, simple and straightforward manner, which does not involve undue experimentation.

The examiner concedes that the specification prophetically considers and discloses general methodologies of making the claimed antibody for *in vivo* therapeutic regimens. However, the examiner does not consider such a disclosure to be enabling, since the examiner contends that the state of β-amyloid aggregation and anti-β-amyloid antibodies is highly unpredictable. The examiner's position is respectfully traversed.

As discussed in the amendment filed February 23, 2004:

> 10D5 antibody has been shown to reduce pathology in a mouse model of Alzheimer's disease, and to cause clearance of plaques *in vivo* in a mouse model of Alzheimer's disease. It has also been reported to be effective at suppressing Aβ deposition and to act as an Aβ sink *in vivo* (see DeMattos et al (2001)[9]). [Footnote Omitted]
>
> As shown in Bard et al (2003); Bard et al (2000);[12] and Bacskai et al (2001)[13] *inter alia*, antibodies 6C6 and 10D5 (again both raised against amino acids 1-28 of Aβ) were effective in clearing Aβ plaques in *in vivo* and *ex vivo* experiments with PDAPP mice. [Footnotes Omitted]

Thus, contrary to the Examiner's apparent contention, inhibition of β-amyloid aggregation and achieving a therapeutic effect is not highly unpredictable using the claimed antibodies.

The examiner's attention is invited to the three patents cited in the Information Disclosure Statement filed on even date herewith, i.e., U.S. Patent 6,743,427 (which claims use of a pharmaceutical composition comprising an antibody that binds to an epitope within residues 1-12 of Aβ); U.S. Patent 6,761,888 (which claims use of a pharmaceutical composition comprising an antibody that binds to an epitope within residues 1-17 of Aβ) and U.S. Patent 6,750,324 (which claims a pharmaceutical composition comprising an antibody that binds to an epitope within residues 1-10 of Aβ). More specifically, reference is made to Examples XI and XII at column 55, line 64, to column 61, line 41, of the U.S. Patent 6,743,427 (which example also appears in the other two patents). These examples show results in animal models of Alzheimer's disease, proving that antibodies that can reduce

aggregation are efficacious in reducing plaque burden. This proves that the antibodies can be used in the manner prophetically described in the present specification. Once it is established that the antibodies of the present invention work as described, it is clear that it is not undue experimentation to determine optimum dosages, etc.

The examiner also contends that the practice of the invention *in vivo* would require new methods of diagnosis as immunocytochemistry cannot be used in humans. However, the examiner's attention is invited to Example XVIII of the '427 patent, beginning at column 67, line 56, through column 68, line 41. This shows how clinical trials would be conducted on humans for similar antibodies. Alzheimer's disease can be diagnosed using ADRDA criteria without the necessity of brain samples. Similarly, as disclosed in the '427 patent, those of ordinary skill in the art are well aware that baseline evaluations of patient function can be made using classic psychometric measures, such as the MMSE, and the ADAS, which is a comprehensive scale for evaluating patients with Alzheimer's disease status and function. These psychometric scales provide a measure of progress of the Alzheimer's condition. Thus, the progression or regression of Alzheimer's disease can be studied without immunocytochemistry.

For all of these reasons, those of ordinary skill in the art would be able to readily make antibodies other than AMY33, and test them in the *in vitro* tests for inhibition of β-amyloid aggregation and maintaining solubility as described in Example 2 of the present specification. Once such

antibodies are identified, it does not require undue experimentation to practice the invention therapeutically as described in the present specification. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

X. Deposit Requirement

Claims 150-167 have been rejected under 35 U.S.C. §112, first paragraph. The examiner states that the invention employs a novel monoclonal antibody AMY33, and deposit is required. This rejection is respectfully traversed.

It is not understood why the examiner characterizes the AMY33 antibody as being novel. The present specification explicitly states that this was a commercially available antibody at the time of the present invention. See column 12, lines 1-5, and column 15, lines 35-36. The specification states that monoclonal antibody AMY33 was purchased from Zymed, San Francisco, California, USA. In the Information Disclosure Statement filed on February 23, 2004[2], applicant submitted two pages from the Zymed Laboratories, Inc. website, showing that this antibody is still commercially available. It should be noted that 37 C.F.R. §1.802(b) states:

> Biological material need not be deposited, *inter alia*, if it known and readily available to the public, or can be made or isolated without undue experimentation.

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[2] It is noted that the examiner has not initialed and returned a copy of the PTO/SB/08a listing the disclosed art that accompanied this IDS. The PAIR records show that the IDS and associated non-patent literature were received by the PTO. Another copy of this form is attached. It is requested that the examiner initial and return this form as it had been timely filed.

Reference is made to MPEP 2404.01 and 2404.02 in this regard.

Note particularly MPEP 2404.01, where it states:

> Unless there is a reasonable basis to believe that the biological material will cease to be available during the enforceable life of the patent, current availability would satisfy the requirement.

Commercial availability is specifically mentioned as a relevant factor in determining whether a biological material is known and readily available to the public. MPEP at 2404.01 specifically states:

> The Office will accept commercial availability as evidence that a biological material is known and readily available only when the evidence is clear and convincing that the public has access to the material. ... A product could be commercially available, but only at a price that effectively eliminates accessibility to those desiring to obtain a sample. The relationship between the applicant relying on a biological material and the commercial supplier is one factor that would be considered in determining whether the biological material was known and readily available. However, the mere fact that the biological material is commercially available only through the patent holder or the patent holder's agents or assigns shall not, by itself, justify a finding that the necessary material is not readily available, absent reason to believe that access to the biological material would later be improperly restricted.

Here, applicant has no relationship whatsoever with Zymed Laboratories, Inc. The website indicates commercial availability to the world at prices that are normally charged for antibodies. Accordingly, for this reason alone, the present rejection should be withdrawn.

However, the rejection should also be withdrawn because the biological material can be made or isolated

without undue experimentation. None of the present claims are directed specifically to AMY33. The specification discloses how to obtain antibodies having the ability to inhibit aggregation and maintain solubility of Aβ, and it has been explained above that they can be made without undue experimentation. In accordance with MPEP 2404.02, no deposit is required where, as here, the required biological materials can be obtained from publicly available material with only routine experimentation and a reliable screening test. For this reason as well, reconsideration and withdrawal of this rejection are respectfully urged.

XI. Written Description Rejection

Claims 150-167 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement of 35 U.S.C. §112. Citing *University of Rochester v Searle*, 69 USPQ2d 1886 (Fed. Cir. 2004), and *Noelle v Lederman*, 69 USPQ2d 1508 (Fed. Cir. 2004), in support of his position, the examiner states that to provide adequate written description and evidence of possession of a claimed genus of antibodies, the specification must provide sufficient distinguishing identifying characteristics of the genus. The examiner concludes that in this case the distinguishing characteristics of the claimed genus of antibodies are not described. This rejection is respectfully traversed.

In *Noelle, supra*, the claims were directed to antibodies specific to any of a genus of CD40CR proteins. The only CD40CR protein fully characterized in the specification was the mouse CD40CR protein. There was no disclosure of the

sequence of the human CD40CR protein, or any of the other CD40CR proteins within the genus. Thus, the inventor could not have been in possession of antibodies to anything except the disclosed mouse CD40CR sequence, and it would have taken undue experimentation to find the sequence for the CD40CR proteins of other species covered by the claim. However, the court acknowledged in *Noelle, supra*, after reviewing *Enzo Biochem v Gen-Probe, Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002), that claims to antibodies specific to a fully characterized antigen fully comply with the written description requirement. Note where *Noelle* states, 69 USPQ2d at 1514:

> Therefore, based on our past precedent, as long as an applicant has disclosed a "*fully characterized antigen*," either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen.

In the present case, the claims are not directed to antibodies that recognize a genus of proteins. Rather, the claims are directed to antibodies which recognize Aβ(1-28). Aβ(1-28) is a fully defined and characterized antigen. Thus, the entire genus of antibodies claimed has written description in the present application. Specifically, claims 150-155 and 162-167 require that the antibodies recognize an epitope within Aβ(1-28), and claims 156-161 require that the antibodies be obtainable using Aβ(1-28) as an immunogen. The 28 residues in question are well-known to those of ordinary skill in the art and are set forth above. Furthermore, as discussed hereinabove, the genus of epitopes within this

sequence can be readily written down by one of ordinary skill in the art.

This situation certainly has no comparison to the situation as in *Noelle, supra,* where only a mouse CD40CR protein is disclosed, and the claims purported to cover antibodies to the corresponding human CD40CR protein and CD40CR proteins of other species. One of ordinary skill in the art reading a specification having only the mouse CD40CR protein would have no idea what is the sequence of the human CD40CR protein. Here, however, one of ordinary skill in the art knows exactly the sequence of Aβ(1-28) and epitopes thereof. As discussed above with respect to the enablement rejection, once these antibodies are made, it is a matter of routine experimentation to assay them for β-amyloid aggregation inhibition using the tests disclosed in the present specification. Therefore, as clearly distinguishable from *Noelle, supra,* the entire genus of antibodies of the present claims is adequately characterized and disclosed in the present specification. The examiner's attention is directed to Example 16 of the Synopsis of Application of the Written Description Guidelines, which states that where the antigen is known and fully characterized (here Aβ(1-28)), the antibody can be claimed generically. Thus, the written description requirement is fully satisfied.

With respect to *Rochester, supra,* relied upon by the examiner, the patent being reviewed in that case did not name even one compound that assays would identify as suitable for practice of the invention, or provide information such that

one skilled in the art could identify a suitable compound. Thus, in that case the inventors could not have been said to have "possessed" the claimed invention without knowing of a compound or method certain to produce said compound. Clearly, this is distinguishable from the present situation, where the examiner concedes that applicant has disclosed one antibody within the genus, AMY-33, and the antigen Aβ(1-28) was well-known in the art. Furthermore, as discussed above in detail, anyone of ordinary skill in the art would be able to raise antibodies against Aβ 1-28, or any epitope therewithin, using ordinary skill in the art without undue experimentation, and then test each positive antibody for its ability to inhibit amyloid aggregation and maintain solubility of Aβ. Thus, the *Rochester* case is not applicable to the present situation. Hence, reconsideration and withdrawal of this rejection is respectfully urged.

XII. Anticipation Rejection over Bickel et al

Claims 150, 151, 156, 157, 162 and 163 have been rejected under 35 U.S.C. §102(a) as being anticipated by Bickel et al. The examiner states that Bickel et al teaches the AMY33 antibody in a solution in 50 mM Tris, pH7.4, and 0.9% NaCl. The examiner states that the recitation "pharmaceutical formulation" is interpreted as an intended use, and is not given patentable weight in this art rejection. This rejection is respectfully traversed.

First of all, as discussed above, all of the claims are directed to pharmaceutical formulations. This term is not merely a statement of intended use, but is a physical form

that is inextricably related to the therapeutic utility. The antibodies of Bickel et al have no stated therapeutic utility. Therefore, the claims are not anticipated by Bickel et al. Furthermore, there is nothing in Bickel et al that would suggest the obviousness of any therapeutic use. Therefore, the present claims also would not be obvious from Bickel et al.

Furthermore, and independently of this reason for lack of anticipation, the examiner recognizes that the Bickel et al formulation includes Tris. Attached hereto as Exhibit C is a material safety data sheet from the website http://www.jtbaker.com/msds/englishhtml/t7112.htm for Tris hydrochloride. It can be seen under "Hazards Identification" that the product is harmful if swallowed, and may cause irritation to skin, eyes, and respiratory tract. With respect to ingestion, it states:

> Mild alkali. May cause irritation and reddening to the mucous membranes of the mouth, esophagus, and gastrointestinal tract. Large oral doses may cause weakness, collapse, and coma.

Thus, a buffer containing Tris is hardly a "pharmaceutically acceptable carrier", as is required by the claims. Hence, the antibody of Bickel et al cannot inherently anticipate the claims. For this reason as well, the claims are not anticipated by Bickel et al. Reconsideration and withdrawal of this rejection are respectfully urged.

XIII. **Anticipation Rejection over Stern et al**

Claims 150, 151, 156, 157, 162 and 163 have been rejected under 35 U.S.C. §102(b) as being anticipated by Stern

et al. The examiner states that Stern et al also teaches the AMY33 antibody in ELISA solution. This rejection is respectfully traversed.

Stern et al does not disclose or make obvious a pharmaceutical formulation. Thus, there can be no anticipation for the same reasons discussed above with respect to Bickel et al.

Furthermore, Stern et al does not use its antibody preparation as a therapeutic, and takes no steps to ensure that the composition would be pharmaceutically acceptable. Indeed, it is apparent that Stern et al used the entire monoclonal antibody supernatant in making his ELISA solution. See page 974 under the heading "Immunohistochemistry", referring to "MAb supernatants". MAb supernatants will include all kinds of proteins made by the hybridoma in addition to the antibody in question. These additional proteins would prevent one from using the composition of Stern et al as a pharmaceutical formulation as claimed in the present application. In view of the fact that there was apparently no attempt to purify the antibody from these accompanying proteins, the resulting ELISA solution cannot be said to be a pharmaceutical formulation comprising an antibody and a pharmaceutically acceptable carrier. Moreover, AMY33, which is commercially available from Sigma, contains sodium azide, which is a poison (see Exhibit D). Thus, this commercially available composition does not contain a pharmaceutically acceptable carrier, cannot be used therapeutically, and is not a pharmaceutical formulation as

claimed in the present application. Reconsideration and withdrawal of this rejection is therefore also respectfully traversed.

XI. Conclusion

It is submitted that all of the claims now present in the case clearly define over the references of record, and fully comply with 35 U.S.C. §112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,
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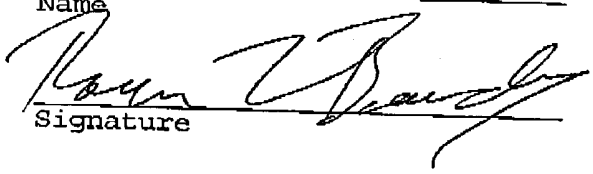

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